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Sulfonamide Allergy and Possible Cross-Reactivity

Helen Kourlas, BS, PharmD, and Susan Morey, PharmD

True allergic reactions are IgE-mediated immune reactions and are also termed type I reactions, where the spectrum of presentation may range from urticaria to severe anaphylactic shock. Currently, 3% of the patients who use sulfonamide antibiotics develop an allergic reaction, with the most common being the development of a maculopapular rash. Sulfonamides are chemical compounds that can be further divided into 3 groups based on differences in their structural makeup. Several cases reviewing

the cross-reactivity between sulfonamide antibiotics and nonantibiotics have suggested an increased risk of cross-reactivity and therefore recommend other treatment strategies to avoid a possible anaphylactic reaction; however, other reports argue that patients with a history of sulfonamide allergy who received sulfonamide nonantibiotics did not experience any adverse reactions. Pertinent data extracted from these studies are reviewed and evaluated.

KEY WORDS: Sulfonamides, hypersensitivity, antibacterial agents, cross-reaction.

WHAT ARE THE PREVALENCES of a sulfonamide allergy and the occurrence of cross-reactivity with structurally similar compounds?

To answer this drug information inquiry, a Medline search was performed via PubMed to obtain all applicable primary literature. The search terms used included sulfonamides, hypersensitivity, antibacterial agents, and cross-reaction. A large amount of literature was available on this topic, and therefore, the search was limited to literature published in human subjects, the English language, reviews, clinical trials, and practice guidelines. Additional references of the articles from the initial search were also read and evaluated when needed.

Approximately 3% of patients who use sulfonamide antibiotics develop an allergic reaction, with the most common being the development of a maculopapular rash.¹⁻³ Sulfonamides are chemical compounds that contain a SO_2NH_2 moiety and can be divided into 3 groups based on their structure.^{1,2} The first group, the sulfonylarylamines, includes the sulfonamide antibiotics. The second group, the nonsulfonylarylamines, includes carbonic anhydrase inhibitors, cyclooxygenase-2 inhibitors, loop diuretics, thiazides, and sulfonylureas, and the protease inhibitors amprenavir and fosamprenavir.^{1,2} The third group is labeled sulfonamide moiety-containing drugs and includes 5-hydroxytryptamine antagonists and other agents, including zonisamide (Figure 1).^{1,2}

LITERATURE REVIEW

Cross-reactivity between the sulfonamide antibiotics and nonantibiotics has been poorly documented over the past 50 years and has remained a topic of debate. Most of the data consist of case reports suggesting that patients who have an allergy to sulfonylarylamines have an increased risk of allergy to a medication in another sulfonamide group.⁷ After Johnson et al's critical review of many of the cases, it was found that other factors may have accounted for the reported cross-reactivity, thus rendering the data

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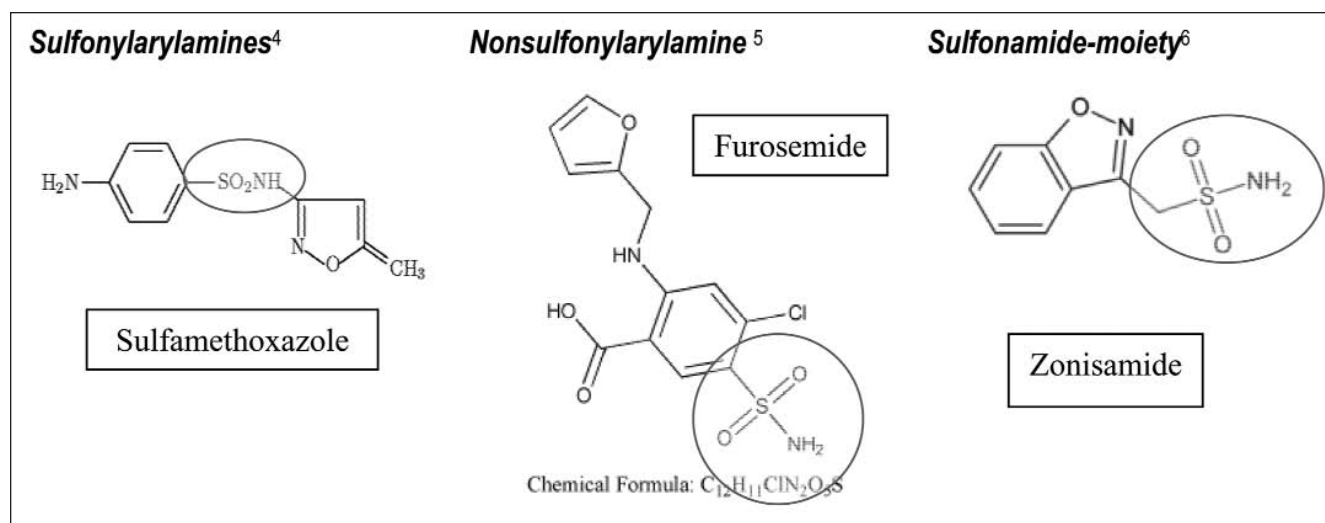


Figure 1. Sulfonfylarylamines, nonsulfonfylarylamines, and sulfonamide-moiety.

inconclusive.³ Johnson et al evaluated literature associated with several sulfonamide drug classes, including carbonic anhydrase inhibitors, sulfonfylureas, loop diuretics, thiazide diuretics, 5-hydroxytryptamine agonists, and cyclooxygenase-2 inhibitors. After review of the carbonic anhydrase inhibitors, a case report by Mosely and Baroody from 1955 was evaluated. In this case, it was reported that a patient with congestive heart failure and prior sulfa allergy experienced an allergic reaction to acetazolamide consisting of gait disturbances, vertigo, facial numbness, and generalized paresthesia. A second administration of acetazolamide 2 days later to this patient provoked the same reaction, in addition to respiratory distress and facial edema. Johnson et al noted that these reactions may have been associated with hypokalemia (potassium level not provided) and caused by a worsening of the patient's heart failure.³

Sulfonfylureas have also been evaluated because of their structure and reports of cross-reactivity. In a survey of 82 clinic patients on a sulfonfylurea, 34 had used a sulfonfylarylamines previously. Seven of these patients reported allergy to sulfonfylarylamines. Of the patients taking a sulfonfylurea, 2 reported a rash. Only 1 of the 2 patients had a previous history of sulfonfylarylamines allergy. This is an observational study, and conclusions must be drawn cautiously; however, the authors of the survey note that it may not be necessary to preclude use of a sulfonfylurea in a patient with sulfonamide allergy. In a review of loop diuretics, a case of hypersensitivity to intravenous furosemide

is discussed where a "sulfonamide"-naïve patient experienced urticaria, periorbital edema and hypotension within 5 minutes of administration of intravenous furosemide. This patient had a history of hydrochlorothiazide use 5 years before this event. The patient also had positive skin tests to chlorothiazide, trimethoprim/sulfamethoxazole, and bumetanide, but not to ethacrynic acid. A review of the case argued that this does not represent cross-reactivity, as the patient had received hydrochlorothiazide in the past with no history of reaction.³ A patient with a history of Stevens-Johnson on trimethoprim/sulfamethoxazole developed a rash with administration of furosemide. A torsemide desensitization protocol in this patient is described in a case report. This case seems to support the concept of cross-reactivity; however, Johnson et al argues that in fact this case is typical of a patient with a serious allergy to one medication being at risk for multiple drug allergies, rather than cross-reactivity.³

In a study by Barrio et al, patients with a history of urticaria and angioedema or a fixed drug eruption from a sulfonfylarylamines were orally challenged with furosemide or procaine. No reactions were observed after administration of furosemide or procaine. Based on their observations, the authors concluded there was no cross-reactivity between furosemide and the sulfonfylureas. When reviewing thiazide diuretics, Johnson et al discussed case reports involving indapamide. A series of 13 patients with skin rash associated with indapamide administration were then administered chlorthalidone, hydrochlorothiazide,

furosemide, epitizide, or clopamide. There was no recurrence of rash in any of the 13 patients. A retrospective chart review of the sulfonamide moiety containing the 5-hydroxytryptamine agonist sumatriptan was conducted in patients with a prior allergic reaction to a sulfonamide. No patient administered sumatriptan reported an adverse event. Several studies have reported on the use of cyclooxygenase-2 inhibitors in patients with a sulfonamide allergy. Three meta-analyses, conducted by Patterson et al, looked at data from 14 randomized controlled trials. Patients with reported sulfonylarylamine allergies and nonsulfonylarylamine allergies who received celecoxib, placebo, or an active comparator were included. In this meta-analysis, there was no statistically significant difference between the 3 groups in terms of potential allergic events. Additionally, patients taking celecoxib with and without other nonsulfonylarylamines were compared. In the last of the 3 meta-analyses, the incidence of allergic reactions with celecoxib was compared with the active comparators. No statistically significant findings were noted in these meta-analyses. Based on these findings, the authors conclude that the risk of cross-reactivity between sulfonamides and celecoxib is low. Based on this review, Johnson et al makes the recommendation that patients with a sulfonylarylamine allergy can be administered medications from the other 2 groups with proper monitoring if it is not possible to use an unrelated product.³

A retrospective cohort study by Strom et al² concluded that a history of sulfonamide antibiotic allergy leads to increased risk of allergy with sulfonamide nonantibiotics; however, they also note that patients with sulfonamide allergies are also at risk for penicillin allergies, suggesting that the risk is not only with sulfonamides. The United Kingdom General Practice Research Database was used to identify patients who were prescribed a sulfonamide antibiotic and then subsequently prescribed a nonantibiotic sulfonamide within 60 days. Patients with an allergic reaction within 30 days of administration of the sulfonamide antibiotic were identified and compared with those from the source group who did not have a reaction. The risk of subsequent allergies to penicillin was also evaluated. The investigators used a narrow definition of allergy (urticaria, anaphylactic shock, erythema multiforme, and drug allergy) and a broad definition of allergy (included asthma, eczema, and unspecified adverse events to a drug). The odds ratio (OR) for association between an allergic reaction after a sulfonamide nonantibiotic and history of allergy to sulfonamide antibiotic compared with no history of allergy was 6.6 (95% confidence interval [CI], 5.2 to 8.4) using the broad definition. Using the narrow

definition, the OR was 13.2 (95% CI, 1.7 to 99.9). The adjusted OR after controlling for sex, age, presence or absence of preexisting asthma, prior asthma medications, or corticosteroids was 2.8 (95% CI, 2.1 to 3.7). The OR for patients who had an allergic reaction to penicillin after a reaction for a sulfonamide antibiotic compared with those with no reaction was 7.8 (95% CI, 7.1 to 8.5) with an adjusted OR of 3.9 (95% CI, 3.5 to 4.3). Based on these findings, it is not clear that an allergy to a sulfonamide antibiotic places a patient at risk specifically for an allergy to a sulfonamide nonantibiotic but rather places the patient at an increased risk of developing an allergy to other medications in general. The investigators concluded that prescribers should be aware that patients with a history of allergic reactions may be at an increased risk for all allergic events related to medications.²

Hemstreet and Page noted that patients with a history of sulfonamide allergy who received sulfonamide nonantibiotics did not experience any adverse events related to the administration of the medication.⁷

ANSWER

A large number of sulfonamide products contain Food and Drug Administration-approved labeling indicating a precaution or contraindication in patients with a "sulfa" allergy. Controversy still exists regarding the validity of data to suggest cross-reactivity between sulfonamide antibiotics and nonantibiotics. Prescribers should still be aware of the cross-reactivity risk and monitor patients carefully when starting a sulfonamide product in a patient with a history of allergy.

DRUG INFORMATION TIP/PEARL

Researching for information has become an easier task with the accessibility and the availability of the Internet. The Internet allows for almost anyone that can operate a computer to log on and "surf" the net. The information can be endless; however, caution should be exercised when retrieving and or drawing conclusions from Web sites discussing medical and pharmacy-related information. A system was developed in 1995 under the Ministry of Health of the State of Geneva called the Health on the Net Foundation Code of Conduct. Their mission is to facilitate the users' ability to distinguish sites that are reliable, relevant, and trustworthy. This is a voluntary service offered by the foundation to authors of Web sites and where membership into the foundation is free.

Web sites are evaluated on the following: qualifications of the author(s) of the site, information that

is complimentary to the doctor/patient relationship, information that is kept confidential, reputable citations that are published, accurate e-mails that are provided, funding sources that are identified, and clear advertising that is separate from the content of the site. The Health on the Net Foundation Code of Conduct is not an award system, and it does not intend to rate the quality of the information provided by a Web site. The purpose however is to hold the developers responsible to the ethical standards necessary to provide information to the public and to assure that the readers are aware of the source and purpose of the Web site.

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